Risk Management Applications From
TGN 1412 Clinical Trial
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"Eight healthy male volunteers were recruited and dosed by Parexel Clinical Pharmacology Research Unit (CPRU) on 13th March 2006. On the same day Serious Adverse Events (SAE's) were reported in 6 of the 8 subjects. According to Parexel CPRU, the subjects experienced 'Cytokine Release Syndrome,' which was reported as 'Life Threatening.' The drug codes ... confirmed that the 6 subjects who experienced SAE's received active drug and the two subjects who did not experience adverse events received placebo."[1]

In the U.S., claims and lawsuits arising from medical research are becoming more frequent. Media coverage over unfortunate results appears robust. Depending on the study, the potential defendants in a lawsuit may include the institution conducting the study, the facility where the study was conducted, the Institutional Review Board (IRB) that approved the study design and informed consent documents, the sponsor of the study, the Contract Research Organization (CRO), and the investigators.

The unfortunate results of the TGN 1412 study provide an object lesson for those who perform human testing of new drugs and medical devices. This article examines some of these lessons, in light of how a similar situation might be litigated, if one were to occur in the United States.

I. Anatomy of a Lawsuit

Clinical trial participants who have filed lawsuits in the United States arising from trial-related injuries have asserted more than a dozen different legal theories. These have included negligence, negligence per se, lack of informed consent, medical malpractice, product liability, infliction of emotional distress, denial of human dignity, violation of constitutional rights, violation of international treaty (e.g., Nuremburg), breach of privacy, battery, fraud, conspiracy, conflict of interest, research misconduct, and breach of contract. Undoubtedly, there have been, or could be, other theories. Had TGN 1412 occurred in the U.S., and been governed by American law, the plaintiff(s) might assert any or all of these theories.

Most of the alleged theories are for negligent conduct in some form by some entity. Accordingly, this article focuses on how the negligence count in a hypothetical lawsuit filed by one or more of the study volunteers might play out, had this situation occurred at a U.S. research site.

A negligence case has four elements:

1. The defendant(s) owed a duty to the plaintiff;

2. The defendant(s) breached that duty;

3. That breach caused the injury that the plaintiff is claiming; and

4. The resulting injury damaged the plaintiff.

A plaintiff must prove each of these elements. Failure to prove even one of the elements prevents a recovery.[2]

The law expresses the notion of duty broadly: everyone should exercise reasonable care in all circumstances. But factually, jurors process the evidence and determine for themselves the specific duties owed in particular circumstances. The duties in a medical or research context are often referred to as the standard of care. Stated in its simplest terms, then, negligence is a finding by the jury that the defendant(s) failed to uphold the standard of care in the circumstances.

In order to guide the jury in determining the standard of care, experts often testify from relevant laws, regulations, guidelines, and industry standards. Examples may include 21 C.F.R. Parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards), Belmont Report on the Protection of Human Subjects, FDA Information Sheets and Good Clinical Practice in FDA-regulated Clinical Trials, PhRMA's Principles for Conduct of Clinical Trials, and international treaties such as the Nuremberg Code and the Declaration of Helsinki.

II. A Hypothetical Negligence Argument

"Clinical trial participants should always be fully informed of the level of risk involved and the degree of uncertainty. Where appropriate, gaining consent from trial participants should involve a "cool-off" period between provision of trial information and giving consent, and/or attendance by a friend or relative of the trial subject. Financial inducements to take part in trials should be considered carefully by the relevant ethics committees and regulators."[3]

45 C.F.R. § 46.116 permits the investigator to seek a subject's consent only under circumstances that provide the person or the representative "sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." 21 C.F.R. § 50.20 suggests that the IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence.

Each volunteer in the TGN 1412 study was paid £2,000 (about $3,600). The question at trial would be whether this amounted to compensation for time and expenses (acceptable), inducement (merits careful consideration), or coercion (unacceptable). Our hypothetical plaintiff might try to establish negligence by arguing that the recruiting methods were coercive. Conversely, the defendant would likely try to characterize the payments as compensation for missed time at work, or for other direct expenses from participating. There is much gray area along this spectrum, but nuanced questions like this are ones that U.S. juries decide regularly in complex negligence cases.

Many position papers and investigative reports published in TGN 1412's aftermath – including the ones mentioned in this article – are publicly available. Going forward, this means that experts can draw upon them when testifying about the standard of care. These resources

have special significance in studies involving monoclonal antibodies, for example in terms of the starting dose:

"It is important to recognise that, during this crucial step of 'first into man' the assessment of antibody toxicity is likely to be less precise than for conventional small molecule drugs. Whatever the protocol for a new antibody therapy, the choice of starting dose is crucial and the design of the initial clinical study must be such that the degree of uncertainty is appropriately taken into account."[4]

III. A Hypothetical Negligence Per Se Argument

Some statutes and regulations are mandatory, which is often to protect the public. Failure to adhere to such mandates may constitute negligence per se. In distinguishing negligence from negligence per se, notice the difference between "should review or consider" versus "shall" or "must not." For the plaintiff, proof that the defendants violated some mandatory law effectively establishes the first two elements of negligence: duty and breach. Stated differently, it is negligence to break the law. From there, the plaintiff need only prove causation and damages.

The following hypothetical example illustrates this point. Under 45 C.F.R. § 46.116(b)(5), when appropriate, a statement shall be provided to subjects "that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject." Suppose that the first two subjects to receive the study drug experienced immediate and profuse sweating. An expert might opine that profuse sweating signaled an unexpected reaction, if not an impending full-blown inflammatory reaction leading to multi-organ failure. Further suppose that the eighth subject was not informed of the unusual sweating that the first two experienced. The plaintiff might try to establish that significant findings were not disclosed, which violated 45 C.F.R. § 46.116(b)(5). From there, the plaintiff might argue negligence simply on proof that the violation caused his injury, i.e., that knowledge of the unusual negative reaction in others would have prompted him to withdraw before receiving the study drug. The defense would likely focus on what are (or are not) "significant new findings" under the circumstances, and what is (or is not) "appropriate" information to provide to subjects.

IV. Sword or Shield

The sources mentioned above establish dozens of substantial requirements for any given study. In our hypothetical U.S. lawsuit, the attorney for the injured subject, with his experts, would mine these sources in search of criticisms. What this attorney or his expert finds, or does not find, would determine the strength of the attack.

One can consider these sources as either a sword or a shield. In this context, a "sword" is like a weapon for assigning blame following an injury. In our legal system, the sword has an advantage of hindsight, of knowing (or, at least having a theory about) what happened. Conversely, thinking of these various laws, requirements, regulatory guidance, and industry standards as a "shield" works like a planning tool. This approach might lead the research entities to anticipate untoward events that could potentially or theoretically happen in their study. They

could then take reasonable steps, if any, to make their occurrence less probable, or supplement the informed consent documents and procedures. When used proactively, this shield leads to safer research, and less exposure to liability. This is why, even if a study volunteer were to be injured, the defense would be strengthened by evidence that this type of planning occurred.

Good risk management requires not only knowledge of the many requirements, but the wisdom to apply them to a particular study, and a system for documenting their application. Good risk management promotes ethical research, and ethical research fosters good risk management.

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[1] *Investigations into adverse incidents during clinical trials of TGN 1412: Background,* Medicines and Healthcare products Regulatory Agency (25 May 2006).
[2] 57 Am Jur 2d, *Negligence*, Section 1 (2004).
[3] *Testing Antibody Therapies Position Paper: Special testing and regulatory considerations for antibody therapies*, The Academy of Medical Sciences (5 April 2006). The position paper can be accessed at http://www.acmedsci.ac.uk/images/publication/SaferMed.pdf.
[4] *Id*.

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